

Metabolism of the extracellular matrix in bronchial asthma (Review)

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2019, Privolzhsky Research Medical University. All rights reserved. Bronchial asthma is associated with upper airway (UA) disorders, primarily with allergic rhinitis, which, in turn, occurs in combination with other UA conditions, including hyperplasia of the nasal mucosa. Chronic rhinosinusitis, if confirmed, is a predictor of asthma severity. The pathogenesis of these diseases includes the remodeling (restructuring) of the extracellular matrix and the adjacent UA structures, which is associated with further worsening of the diseases and their resistance to therapy. It is known that remodeling of the lower respiratory tract in bronchial asthma is characterized by epithelial desquamation, hyperplasia of goblet cells, thickening of the basement membrane, fibrosis of the subepithelium, hyperplasia of smooth muscles of the respiratory tract, and increased angiogenesis. At the same time, the UA remodeling in patients with asthma is still poorly understood; the data are still limited and often contradict each other. With isolated allergic rhinitis, the remodeling process is not very much pronounced and is limited, apparently, to a basement membrane thickening. In chronic rhinosinusitis, the UA remodeling manifests by epithelial hyperplasia and an increased sedimentation and degradation of the matrix along with the accumulation of plasma proteins. Despite recent extensive studies, the cellular and molecular mechanisms involved in the respiratory tract remodeling remain largely undetermined, which necessitates further research into these processes. The review addresses several aspects of neuro-humoral control of the extracellular matrix metabolism and the associated remodeling of the upper and lower airway in patients with asthma.

<http://dx.doi.org/10.17691/stm2018.10.4.25>

Keywords

Allergic rhinitis, Bronchial asthma, Chronic rhinosinusitis, Extracellular matrix, Remodeling

References

- [1] Theocharis A.D., Skandalis S.S., Gialeli C., Karamanos N.K. Extracellular matrix structure. *Adv Drug Deliv Rev* 2016; 97: 4-27, <https://doi.org/10.1016/j.addr.2015.11.001>.
- [2] LeMessurier K.S., Palipane M., Tiwary M., Gavin B., Samarasinghe A.E. Chronic features of allergic asthma are enhanced in the absence of resistin-like molecule-beta. *Sci Rep* 2018; 8(1): 7061, <https://doi.org/10.1038/s41598-018-25321-y>.
- [3] Gu B.H., Madison M.C., Corry D., Kheradmand F. Matrix remodeling in chronic lung diseases. *Matrix Biol* 2018, 73: 52-63, <https://doi.org/10.1016/j.matbio.2018.03.012>.

- [4] Annoni R., Lancas T., Yukimatsu Tanigawa R., de Medeiros Matsushita M., de Moraes Fernandez S., Bruno A., Fernando Ferraz da Silva L., Roughley P.J., Battaglia S., Dolhnikoff M., Hiemstra P.S., Sterk P.J., Rabe K.F., Mauad T. Extracellular matrix composition in COPD. *Eur Respir J* 2012; 40(6): 1362-1373, <https://doi.org/10.1183/09031936.00192611>.
- [5] Samitas K., Carter A., Kariyawasam H.H., Xanthou G. Upper and lower airway remodelling mechanisms in asthma, allergic rhinitis and chronic rhinosinusitis: the one airway concept revisited. *Allergy* 2018; 73(5): 993-1002, <https://doi.org/10.1111/all.13373>.
- [6] Weitoft M., Andersson C., Andersson-Sjoland A., Tufvesson E., Bjermer L., Erjefalt J., Westergren-Thorsson G. Controlled and uncontrolled asthma display distinct alveolar tissue matrix compositions. *Respir Res* 2014; 15: 67, <https://doi.org/10.1186/1465-9921-15-67>.
- [7] Wight T.N., Frevert C.W., Debley J.S., Reeves S.R., Parks W.C., Ziegler S.F. Interplay of extracellular matrix and leukocytes in lung inflammation. *Cell Immunol* 2017; 312: 1-14, <https://doi.org/10.1016/j.cellimm.2016.12.003>.
- [8] Grzela K., Zagorska W., Krejner A., Litwiniuk M., Zawadzka-Krajewska A., Banaszkiwicz A., Kulus M., Grzela T. Prolonged treatment with inhaled corticosteroids does not normalize high activity of matrix metalloproteinase-9 in exhaled breath condensates of children with asthma. *Arch Immunol Ther Exp (Warsz)* 2015; 63(3): 231-237, <https://doi.org/10.1007/s00005-015-0328-z>.
- [9] Mouw J.K., Ou G., Weaver V.M. Extracellular matrix assembly: a multiscale deconstruction. *Nat Rev Mol Cell Biol* 2014; 15(12): 771-785, <https://doi.org/10.1038/nrm3902>.
- [10] Pozzi A., Yurchenco P.D., Iozzo R.V. The nature and biology of basement membranes. *Matrix Biol* 2017; 57-58: 1-11, <https://doi.org/10.1016/j.matbio.2016.12.009>.
- [11] Hohenester E., Yurchenco P.D. Laminins in basement membrane assembly. *Cell Adh Migr* 2013; 7(1): 56-63, <https://doi.org/10.4161/cam.21831>.
- [12] Timpl R., Brown J.C. Supramolecular assembly of basement membranes. *Bioessays* 1996; 18(2): 123-132, <https://doi.org/10.1002/bies.950180208>.
- [13] Dziadek M. Role of laminin-nidogen complexes in basement membrane formation during embryonic development. *Experientia* 1995; 51(9-10): 901-913, <https://doi.org/10.1007/bf01921740>.
- [14] Sonbol H.S. Extracellular matrix remodeling in human disease. *J Microsc Ultrastruct* 2018; 6(3): 123-128, https://doi.org/10.4103/jmau.jmau_4_18.
- [15] LeBleu V.S., MacDonald B., Kalluri R. Structure and function of basement membranes. *Exp Biol Med (Maywood)* 2007; 232(9): 1121-1129, <https://doi.org/10.3181/0703-mr-72>.
- [16] Halfter W., Oertle P., Monnier C.A., Camenzind L., Reyes-Lua M., Hu H., Candiello J., Labilloy A., Balasubramani M., Henrich P.B., Plodinec M. New concepts in basement membrane biology. *FEBS J* 2015; 282(23): 4466-4479, <https://doi.org/10.1111/febs.13495>.
- [17] Behrens D.T., Villone D., Koch M., Brunner G., Sorokin L., Robenek H., Bruckner-Tuderman L., Bruckner P., Hansen U. The epidermal basement membrane is a composite of separate laminin- or collagen IV-containing networks connected by aggregated perlecan, but not by nidogens. *J Biol Chem* 2012; 287(22): 18700-18709, <https://doi.org/10.1074/jbc.M111.336073>.
- [18] Fernandes D.J., Bonacci J.V., Stewart A.G. Extracellular matrix, integrins, and mesenchymal cell function in the airways. *Curr Drug Targets* 2006; 7(5): 567-577.
- [19] Hansen S.W., Ohtani K., Roy N., Wakamiya N. The collectins CL-L1, CL-K1 and CL-P1, and their roles in complement and innate immunity. *Immunobiology* 2016; 221(10): 1058-1067, <https://doi.org/10.1016/j.imbio.2016.05.012>.
- [20] Kubysheva N., Soodaeva S., Novikov V., Eliseeva T., Li T., Klimanov I., Kuzmina E., Baez-Medina H., Solovyev V., Ovsyannikov D.Y., Batyrshin I. Soluble HLA-I and HLA-II molecules are potential prognostic markers of progression of systemic and local inflammation in patients with COPD. *Disease Markers* 2018; 2018: 1-7, <https://doi.org/https://doi.org/10.1155/2018/3614341>.
- [21] Barnes P.J. Cellular and molecular mechanisms of asthma and COPD. *Clin Sci (Lond)* 2017; 131(13): 1541-1558, <https://doi.org/10.1042/CS20160487>.
- [22] Burgess J.K., Ceresa C., Johnson S.R., Kanabar V., Moir L.M., Nguyen T.T., Oliver B.G., Schuliga M., Ward J. Tissue and matrix influences on airway smooth muscle function. *Pulm Pharmacol Ther* 2009; 22(5): 379-387, <https://doi.org/10.1016/j.pupt.2008.12.007>.
- [23] Sapir L., Tzili S. Talking over the extracellular matrix: how do cells communicate mechanically? *Semin Cell Dev Biol* 2017; 71: 99-105, <https://doi.org/10.1016/j.semcdb.2017.06.010>.
- [24] Wells J.M., Gaggari A., Blalock J.E. MMP generated matrikines. *Matrix Biol* 2015; 44-46: 122-129, <https://doi.org/10.1016/j.matbio.2015.01.016>.
- [25] Ricard-Blum S., Salza R. Matricryptins and matrikines: biologically active fragments of the extracellular matrix. *Exp Dermatol* 2014; 23(7): 457-463, <https://doi.org/10.1111/exd.12435>.
- [26] Jarvelainen H., Sainio A., Koulou M., Wight T.N., Penttinen R. Extracellular matrix molecules: potential targets in pharmacotherapy. *Pharmacol Rev* 2009; 61(2): 198-223, <https://doi.org/10.1124/pr.109.001289>.

- [27] Burgess J.K., Mauad T., Tjin G., Karlsson J.C., Westergren-Thorsson G. The extracellular matrix — the under-recognized element in lung disease? *J Pathol* 2016; 240(4): 397–409, <https://doi.org/10.1002/path.4808>.
- [28] Liu G., Cooley M.A., Nair P.M., Donovan C., Hsu A.C., Jarnicki A.G., Haw T.J., Hansbro N.G., Ge Q., Brown A.C., Tay H., Foster P.S., Wark P.A., Horvat J.C., Bourke J.E., Grainge C.L., Argraves W.S., Oliver B.G., Knight D.A., Burgess J.K., Hansbro P.M. Airway remodelling and inflammation in asthma are dependent on the extracellular matrix protein fibulin-1c. *J Pathol* 2017; 243(4): 510–523, <https://doi.org/10.1002/path.4979>.
- [29] White E.S. Lung extracellular matrix and fibroblast function. *Ann Am Thorac Soc* 2015; 12(Suppl 1): S30–S33, <https://doi.org/10.1513/annalsats.201406-240mg>.
- [30] Pawankar R., Nonaka M. Inflammatory mechanisms and remodeling in chronic rhinosinusitis and nasal polyps. *Curr Allergy Asthma Rep* 2007; 7(3): 202–208.
- [31] Watelet J.B., Dogne J.M., Mullier F. Remodeling and repair in rhinosinusitis. *Curr Allergy Asthma Rep* 2015; 15(6): 34, <https://doi.org/10.1007/s11882-015-0531-3>.
- [32] Boulet L.P. Airway remodeling in asthma: update on mechanisms and therapeutic approaches. *Curr Opin Pulm Med* 2018; 24(1): 56–62, <https://doi.org/10.1097/MCP.0000000000000441>.
- [33] Bonnans C., Chou J., Werb Z. Remodelling the extracellular matrix in development and disease. *Nat Rev Mol Cell Biol* 2014; 15(12): 786–801, <https://doi.org/10.1038/nrm3904>.
- [34] Cox T.R., Erler J.T. Remodeling and homeostasis of the extracellular matrix: implications for fibrotic diseases and cancer. *Dis Model Mech* 2011; 4(2): 165–178, <https://doi.org/10.1242/dmm.004077>.
- [35] Smith H.W., Marshall C.J. Regulation of cell signalling by uPAR. *Nat Rev Mol Cell Biol* 2010; 11(1): 23–36, <https://doi.org/10.1038/nrm2821>.
- [36] Giuffrida P., Biancheri P., MacDonald T.T. Proteases and small intestinal barrier function in health and disease. *Curr Opin Gastroenterol* 2014; 30(2): 147–153, <https://doi.org/10.1097/MOG.0000000000000042>.
- [37] Rawlings N.D., Waller M., Barrett A.J., Bateman A. MEROPS: the database of proteolytic enzymes, their substrates and inhibitors. *Nucleic Acids Res* 2014; 42(D1): D503–D509, <https://doi.org/10.1093/nar/gkt953>.
- [38] Murphy G. Riding the metalloproteinase roller coaster. *J Biol Chem* 2017; 292(19): 7708–7718, <https://doi.org/10.1074/jbc.x117.785295>.
- [39] Jones G.C., Riley G.P. ADAMTS proteinases: a multi-domain, multi-functional family with roles in extracellular matrix turnover and arthritis. *Arthritis Res Ther* 2005; 7(4): 160–169, <https://doi.org/10.1186/ar1783>.
- [40] Krouse J.H. Asthma management for the otolaryngologist. *Otolaryngol Clin North Am* 2017; 50(6): 1065–1076, <https://doi.org/10.1016/j.otc.2017.08.006>.
- [41] Broder C., Arnold P., Vadon-Le Goff S., Konerding M.A., Bahr K., Muller S., Overall C.M., Bond J.S., Koudelka T., Tholey A., Hulmes D.J., Moali C., Becker-Paully C. Metalloproteinases meprin alpha and meprin beta are C- and N-procollagen proteinases important for collagen assembly and tensile strength. *Proc Natl Acad Sci USA* 2013; 110(35): 14219–14224, <https://doi.org/10.1073/pnas.1305464110>.
- [42] Prakash Y.S. Airway smooth muscle in airway reactivity and remodeling: what have we learned? *Am J Physiol Lung Cell Mol Physiol* 2013; 305(12): L912–L933, <https://doi.org/10.1152/ajplung.00259.2013>.
- [43] Al-Muhsen S., Johnson J.R., Hamid Q. Remodeling in asthma. *J Allergy Clin Immunol* 2011; 128(3): 451–462, <https://doi.org/10.1016/j.jaci.2011.04.047>.
- [44] Tschumperlin D.J. Physical forces and airway remodeling in asthma. *N Engl J Med* 2011; 364(21): 2058–2059, <https://doi.org/10.1056/NEJMe1103121>.
- [45] Fehrenbach H., Wagner C., Wegmann M. Airway remodeling in asthma: what really matters. *Cell Tissue Res* 2017; 367(3): 551–569, <https://doi.org/10.1007/s00441-016-2566-8>.
- [46] Payne D.N., Rogers A.V., Adelroth E., Bandi V., Guntupalli K.K., Bush A., Jeffery P.K. Early thickening of the reticular basement membrane in children with difficult asthma. *Am J Respir Crit Care Med* 2003; 167(1): 78–82, <https://doi.org/10.1164/rccm.200205-414oc>.
- [47] Pohunek P., Warner J.O., Turzikova J., Kudrman J., Roche W.R. Markers of eosinophilic inflammation and tissue re-modelling in children before clinically diagnosed bronchial asthma. *Pediatr Allergy Immunol* 2005; 16(1): 43–51, <https://doi.org/10.1111/j.1399-3038.2005.00239.x>.
- [48] Elliot J.G., Noble P.B., Mauad T., Bai T.R., Abramson M.J., McKay K.O., Green F.H.Y., James A.L. Inflammation-dependent and independent airway remodelling in asthma. *Respirology* 2018; 23(12): 1138–1145, <https://doi.org/10.1111/resp.13360>.
- [49] Kicic A., Sutanto E.N., Stevens P.T., Knight D.A., Stick S.M. Intrinsic biochemical and functional differences in bronchial epithelial cells of children with asthma. *Am J Respir Crit Care Med* 2006; 174(10): 1110–1118, <https://doi.org/10.1164/rccm.200603-392oc>.
- [50] James A.L., Bai T.R., Mauad T., Abramson M.J., Dolhnikoff M., McKay K.O., Maxwell P.S., Elliot J.G., Green F.H. Airway smooth muscle thickness in asthma is related to severity but not duration of asthma. *Eur Respir J* 2009; 34(5): 1040–1045, <https://doi.org/10.1183/09031936.00181608>.

- [51] Prakash Y.S., Halayko A.J., Gosens R., Panettieri R.A. Jr., Camoretti-Mercado B., Penn R.B. An official American Thoracic Society research statement: current challenges facing research and therapeutic advances in airway remodeling. *Am J Respir Crit Care Med* 2017; 195(2): e4-e19, <https://doi.org/10.1164/rccm.201611-2248st>.
- [52] Huber H.L., Koessler K.K. The pathology of bronchial asthma. *Arch Intern Med* 1922; 30(6): 689-760, <https://doi.org/10.1001/archinte.1922.00110120002001>.
- [53] Pascoe C.D., Seow C.Y., Hackett T.L., Pare P.D., Donovan G.M. Heterogeneity of airway wall dimensions in humans: a critical determinant of lung function in asthmatics and nonasthmatics. *Am J Physiol Lung Cell Mol Physiol* 2017; 312(3): L425-L431, <https://doi.org/10.1152/ajplung.00421.2016>.
- [54] Poon A.H., Hamid Q. Severe asthma: have we made progress? *Ann Am Thorac Soc* 2016; 13(Suppl 1): S68-S77.
- [55] Huang J., Olivenstein R., Taha R., Hamid Q., Ludwig M. Enhanced proteoglycan deposition in the airway wall of atopic asthmatics. *Am J Respir Crit Care Med* 1999; 160(2): 725-729, <https://doi.org/10.1164/ajrccm.160.2.9809040>.
- [56] Ward C., Reid D.W., Orsida B.E., Feltis B., Ryan V.A., Johns D.P., Walters E.H. Inter-relationships between airway inflammation, reticular basement membrane thickening and bronchial hyper-reactivity to methacholine in asthma; a systematic bronchoalveolar lavage and airway biopsy analysis. *Clin Exp Allergy* 2005; 35(12): 1565-1571, <https://doi.org/10.1111/j.1365-2222.2005.02365.x>.
- [57] Davies D.E. The role of the epithelium in airway remodeling in asthma. *Proc Am Thorac Soc* 2009; 6(8): 678-682, <https://doi.org/10.1513/pats.200907-067dp>.
- [58] Holgate S.T., Wenzel S., Postma D.S., Weiss S.T., Renz H., Sly P.D. Asthma. *Nat Rev Dis Primers* 2015; 1: 15025, <https://doi.org/10.1038/nrdp.2015.25>.
- [59] Holgate S.T. Mechanisms of asthma and implications for its prevention and treatment: a personal journey. *Allergy Asthma Immunol Res* 2013; 5(6): 343-347, <https://doi.org/10.4168/aaair.2013.5.6.343>.
- [60] Nayak A.P., Deshpande D.A., Penn R.B. New targets for resolution of airway remodeling in obstructive lung diseases. *F1000Res* 2018; 7: 680, <https://doi.org/10.12688/f1000research.14581.1>.
- [61] Chan V., Burgess J.K., Ratoff J.C., O'Connor B.J., Greenough A., Lee T.H., Hirst S.J. Extracellular matrix regulates enhanced eotaxin expression in asthmatic airway smooth muscle cells. *Am J Respir Crit Care Med* 2006; 174(4): 379-385, <https://doi.org/10.1164/rccm.200509-1420oc>.
- [62] Lauzon A.M., Martin J.G. Airway hyperresponsiveness; smooth muscle as the principal actor. *F1000Res* 2016; 5: 306, <https://doi.org/10.12688/f1000research.7422.1>.
- [63] Grainge C.L., Lau L.C., Ward J.A., Dulay V., Lahiff G., Wilson S., Holgate S., Davies D.E., Howarth P.H. Effect of bronchoconstriction on airway remodeling in asthma. *N Engl J Med* 2011; 364(21): 2006-2015, <https://doi.org/10.1056/nejmoa1014350>.
- [64] Gosens R., Grainge C. Bronchoconstriction and airway biology: potential impact and therapeutic opportunities. *Chest* 2015; 147(3): 798-803, <https://doi.org/10.1378/chest.14-1142>.
- [65] Dogan M., Han Y.S., Delmotte P., Sieck G.C. TNFalpha enhances force generation in airway smooth muscle. *Am J Physiol Lung Cell Mol Physiol* 2017; 312(6): L994-L1002, <https://doi.org/10.1152/ajplung.00550.2016>.
- [66] Burgess J.K., Ge Q., Boustany S., Black J.L., Johnson P.R. Increased sensitivity of asthmatic airway smooth muscle cells to prostaglandin E2 might be mediated by increased numbers of E-prostanoid receptors. *J Allergy Clin Immunol* 2004; 113(5): 876-881, <https://doi.org/10.1016/j.jaci.2004.02.029>.
- [67] Brightling C.E., Bradding P. The re-emergence of the mast cell as a pivotal cell in asthma pathogenesis. *Curr Allergy Asthma Rep* 2005; 5(2): 130-135, <https://doi.org/10.1007/s11882-005-0086-9>.
- [68] Niimi A., Matsumoto H., Amitani R., Nakano Y., Sakai H., Takemura M., Ueda T., Chin K., Itoh H., Ingenito E.P., Mishima M. Effect of short-term treatment with inhaled corticosteroid on airway wall thickening in asthma. *Am J Med* 2004; 116(11): 725-731, <https://doi.org/10.1016/j.amjmed.2003.11.026>.
- [69] Walker J.K.L., Theriot B.S., Ghio M., Trempus C.S., Wong J.E., McQuade V.L., Liang J., Jiang D., Noble P.W., Garantziotis S., Kraft M., Ingram J.L. Targeted HAS2 expression lessens airway responsiveness in chronic murine allergic airway disease. *Am J Respir Cell Mol Biol* 2017; 57(6): 702-710, <https://doi.org/10.1165/rcmb.2017-0095oc>.
- [70] Kruse M.N., Becker C., Lottaz D., Köhler D., Yiallourous I., Krell H.W., Sterchi E.E., Stöcker W. Human meprin alpha and beta homo-oligomers: cleavage of basement membrane proteins and sensitivity to metalloprotease inhibitors. *Biochem J* 2004; 378(Pt 2): 383-389, <https://doi.org/10.1042/bj20031163>.
- [71] Bougault V., Loubaki L., Joubert P., Turmel J., Couture C., Laviolette M., Chakir J., Boulet L.P. Airway remodeling and inflammation in competitive swimmers training in indoor chlorinated swimming pools. *J Allergy Clin Immunol* 2012; 129(2): 351-358.e1, <https://doi.org/10.1016/j.jaci.2011.11.010>.
- [72] ten Brinke A. Risk factors associated with irreversible airflow limitation in asthma. *Curr Opin Allergy Clin Immunol* 2008; 8(1): 63-69, <https://doi.org/10.1097/aci.0b013e3282f3b5b5>.
- [73] Lange P., Parner J., Vestbo J., Schnohr P., Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339(17): 1194-1200, <https://doi.org/10.1056/nejm199810223391703>.

- [74] Niimi A., Matsumoto H., Takemura M., Ueda T., Chin K., Mishima M. Relationship of airway wall thickness to airway sensitivity and airway reactivity in asthma. *Am J Respir Crit Care Med* 2003; 168(8): 983-988, <https://doi.org/10.1164/rccm.200211-1268oc>.
- [75] McParland B.E., Macklem P.T., Pare P.D. Airway wall remodeling: friend or foe? *J Appl Physiol* 2003; 95(1): 426- 434, <https://doi.org/10.1152/jappphysiol.00159.2003>.
- [76] Lezmi G., Gosset P., Deschildre A., Abou-Taam R., Mahut B., Beydon N., de Blic J. Airway Remodeling in preschool children with severe recurrent wheeze. *Am J Respir Crit Care Med* 2015; 192(2): 164-171, <https://doi.org/10.1164/rccm.201411-1958oc>.
- [77] Chakir J., Laviolette M., Boutet M., Laliberté R., Dubé J., Boulet L.P. Lower airways remodeling in nonasthmatic subjects with allergic rhinitis. *Lab Invest* 1996; 75(5): 735-744.
- [78] Tillie-Leblond I., de Blic J., Jaubert F., Wallaert B., Scheinmann P., Gosset P. Airway remodeling is correlated with obstruction in children with severe asthma. *Allergy* 2008; 63(5): 533-541, <https://doi.org/10.1111/j.1398-9995.2008.01656.x>.
- [79] O'Reilly R., Ullmann N., Irving S., Bossley C.J., Sonnappa S., Zhu J., Oates T., Banya W., Jeffery P.K., Bush A., Saglani S. Increased airway smooth muscle in preschool wheezers who have asthma at school age. *J Allergy Clin Immunol* 2013; 131(4): 1024-1032.e16, <https://doi.org/10.1016/j.jaci.2012.08.044>.
- [80] Owens L., Laing I.A., Zhang G., Le Souef P.N. Infant lung function predicts asthma persistence and remission in young adults. *Respirology* 2017; 22(2): 289-294, <https://doi.org/10.1111/resp.12901>.
- [81] Williams R.C., Skelton A.J., Todryk S.M., Rowan A.D., Preshaw P.M., Taylor J.J. Leptin and pro-inflammatory stimuli synergistically upregulate MMP-1 and MMP-3 secretion in human gingival fibroblasts. *PLoS One* 2016; 11(2): e0148024, <https://doi.org/10.1371/journal.pone.0148024>.
- [82] Sicard D., Haak A.J., Choi K.M., Craig A.R., Fredenburgh L.E., Tschumperlin D.J. Aging and anatomical variations in lung tissue stiffness. *Am J Physiol Lung Cell Mol Physiol* 2018; 314(6): L946-L955, <https://doi.org/10.1152/ajplung.00415.2017>.
- [83] Russell R.E., Culpitt S.V., DeMatos C., Donnelly L., Smith M., Wiggins J., Barnes P.J. Release and activity of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 by alveolar macrophages from patients with chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2002; 26(5): 602-609, <https://doi.org/10.1165/ajrcmb.26.5.4685>.
- [84] Todorova L., Gurcan E., Miller-Larsson A., Westergren-Thorsson G. Lung fibroblast proteoglycan production induced by serum is inhibited by budesonide and formoterol. *Am J Respir Cell Mol Biol* 2006; 34(1): 92-100, <https://doi.org/10.1165/rcmb.2005-0048oc>.
- [85] Eliseeva T.I., Geppe N.A., Tush E.V., Khaletskaya O.V., Balabolkin I.I., Bulgakova V.A., Kubysheva N.I., Ignatov S.K. Body height of children with bronchial asthma of various severities. *Can Respir J* 2017; 2017: 8761404, <https://doi.org/10.1155/2017/8761404>.
- [86] Eliseeva T.I., Geppe N.A., Ignatov S.K., Soodaeva S.K., Tush E.V., Khaletskaya O.V., Potemina T.E., Malakhov A.B., Kubysheva N.I., Solovyov V.A. Relative body mass index as a new tool for nutritional status assessment in children and adolescents with bronchial asthma. *Sovremennye tehnologii v medicine* 2017; 9(1): 135-148, <https://doi.org/10.17691/stm2017.9.1.18>.
- [87] Tushch E.V., Eliseeva T.I., Balabolkin I.I., Bulgakova V.A., Khaletskaya O.V., Shchukina D.A., Romanova N.V., Malyshev I.S., Kuzmichev K.V., Potemina T.E., Novikova N.A., Prakhov A.V. Peculiarities of physical development of children and adolescents having bronchial asthma. *Medicinskij al'manah* 2017; (2): 52-56, <https://doi.org/10.21145/2499-9954-2017-2-52-56>.
- [88] Zhang Z., Wang F., Wang B.J., Chu G., Cao Q., Sun B.G., Dai Q.Y. Inhibition of leptin-induced vascular extracellular matrix remodelling by adiponectin. *J Mol Endocrinol* 2014; 53(2): 145-154, <https://doi.org/10.1530/jme-14-0027>.
- [89] Arteaga-Solis E., Zee T., Emala C.W., Vinson C., Wess J., Karsenty G. Inhibition of leptin regulation of parasympathetic signaling as a cause of extreme body weight-associated asthma. *Cell Metab* 2013; 17(1): 35-48, <https://doi.org/10.1016/j.cmet.2012.12.004>.
- [90] Deshpande M., Papp S., Schaffer L., Pouyani T. Hydrocortisone and triiodothyronine regulate hyaluronate synthesis in a tissue-engineered human dermal equivalent through independent pathways. *J Biosci Bioeng* 2015; 119(2): 226-236, <https://doi.org/10.1016/j.jbiosc.2014.08.001>.
- [91] Cayrol F., Diaz Flaque M.C., Fernando T., Yang S.N., Sterle H.A., Bolontrade M., Amoros M., Isse B., Farias R.N., Ahn H., Tian Y.F., Tabbo F., Singh A., Inghirami G., Cerchiatti L., Cremaschi G.A. Integrin alphavbeta3 acting as membrane receptor for thyroid hormones mediates angiogenesis in malignant T cells. *Blood* 2015; 125(5): 841-851, <https://doi.org/10.1182/blood-2014-07-587337>.
- [92] Wenzel S.E., Robinson C.B., Leonard J.M., Panettieri R.A. Jr. Nebulized dehydroepiandrosterone-3-sulfate improves asthma control in the moderate-to-severe asthma results of a 6-week, randomized, double-blind, placebo-controlled study. *Allergy Asthma Proc* 2010; 31(6): 461-471, <https://doi.org/10.2500/aap.2010.31.3384>.
- [93] Nair P., Radford K., Fanat A., Janssen L.J., Peters-Golden M., Cox P.G. The effects of leptin on airway smooth muscle responses. *Am J Respir Cell Mol Biol* 2008; 39(4): 475-481, <https://doi.org/10.1165/rcmb.2007-0091oc>.

- [94] Gupta A., Sjoukes A., Richards D., Banya W., Hawrylowicz C., Bush A., Saglani S. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. *Am J Respir Crit Care Med* 2011; 184(12): 1342-1349, <https://doi.org/10.1164/rccm.201107-1239oc>.
- [95] Gosens R., Nelemans S.A., Hiemstra M., Grootte Bromhaar M.M., Meurs H., Zaagsma J. Insulin induces a hypercontractile airway smooth muscle phenotype. *Eur J Pharmacol* 2003; 481(1): 125-131, <https://doi.org/10.1016/j.ejphar.2003.08.081>.
- [96] Degano B., Mourlanette P., Valmary S., Pontier S., Prevost M.C., Escamilla R. Differential effects of low and high-dose estradiol on airway reactivity in ovariectomized rats. *Respir Physiol Neurobiol* 2003; 138(2-3): 265-274, <https://doi.org/10.1016/j.resp.2003.08.007>.
- [97] Carlson C.L., Cushman M., Enright P.L., Cauley J.A., Newman A.B. Hormone replacement therapy is associated with higher FEV1 in elderly women. *Am J Respir Crit Care Med* 2001; 163(2): 423-428, <https://doi.org/10.1164/ajrccm.163.2.2003040>.
- [98] Montaña L.M., Espinoza J., Flores-Soto E., Chávez J., Perusquía M. Androgens are bronchoactive drugs that act by relaxing airway smooth muscle and preventing bronchospasm. *J Endocrinol* 2014; 222(1): 1-13, <https://doi.org/10.1530/joe-14-0074>.
- [99] Bordallo J., de Boto M.J., Meana C., Velasco L., Bordallo C., Suárez L., Cantabrana B., Sánchez M. Modulatory role of endogenous androgens on airway smooth muscle tone in isolated guinea-pig and bovine trachea; involvement of beta2-adrenoceptors, the polyamine system and external calcium. *Eur J Pharmacol* 2008; 601(1-3): 154-162, <https://doi.org/10.1016/j.ejphar.2008.10.039>.
- [100] Ishida-Takahashi R., Uotani S., Abe T., Degawa-Yamauchi M., Fukushima T., Fujita N., Sakamaki H., Yamasaki H., Yamaguchi Y., Eguchi K. Rapid inhibition of leptin signaling by glucocorticoids in vitro and in vivo. *J Biol Chem* 2004; 279(19): 19658-19664, <https://doi.org/10.1074/jbc.m310864200>.
- [101] Kistemaker L.E., Oenema T.A., Meurs H., Gosens R. Regulation of airway inflammation and remodeling by muscarinic receptors: perspectives on anticholinergic therapy in asthma and COPD. *Life Sci* 2012; 91(21-22): 1126-1133, <https://doi.org/10.1016/j.lfs.2012.02.021>.
- [102] Matthiesen S., Bahulayan A., Kempkens S., Haag S., Fuhrmann M., Stichnote C., Juergens U.R., Racke K. Muscarinic receptors mediate stimulation of human lung fibroblast proliferation. *Am J Respir Cell Mol Biol* 2006; 35(6): 621-627, <https://doi.org/10.1165/rcmb.2005-0343rc>.
- [103] Haag S., Matthiesen S., Juergens U.R., Racke K. Muscarinic receptors mediate stimulation of collagen synthesis in human lung fibroblasts. *Eur Respir J* 2008; 32(3): 555-562, <https://doi.org/10.1183/09031936.00129307>.
- [104] Jia Y., Yue Y., Hu D.N., Chen J.L., Zhou J.B. Human aqueous humor levels of transforming growth factor-beta2: association with matrix metalloproteinases/tissue inhibitors of matrix metalloproteinases. *Biomed Rep* 2017; 7(6): 573-578, <https://doi.org/10.3892/br.2017.1004>.
- [105] Eliseeva T.I., Balabolkin I.I. Modern technologies of bronchial asthma control in children (review). *Sovremennye tehnologii v medicine* 2015; 7(2): 168-184, <https://doi.org/10.17691/stm2015.7.2.21>.
- [106] Buels K.S., Jacoby D.B., Fryer A.D. Non-bronchodilating mechanisms of tiotropium prevent airway hyperreactivity in a guinea-pig model of allergic asthma. *Br J Pharmacol* 2012; 165(5): 1501-1514, <https://doi.org/10.1111/j.1476-5381.2011.01632.x>.
- [107] Asano K., Shikama Y., Shoji N., Hirano K., Suzuki H., Nakajima H. Tiotropium bromide inhibits TGF-beta-induced MMP production from lung fibroblasts by interfering with Smad and MAPK pathways in vitro. *Int J Chron Obstruct Pulmon Dis* 2010; 5: 277-286, <https://doi.org/10.2147/copd.s11737>.
- [108] Pera T., Zuidhof A., Valadas J., Smit M., Schoemaker R.G., Gosens R., Maarsingh H., Zaagsma J., Meurs H. Tiotropium inhibits pulmonary inflammation and remodelling in a guinea pig model of COPD. *Eur Respir J* 2011; 38(4): 789-796, <https://doi.org/10.1183/09031936.00146610>.
- [109] Bousquet J., Arnavielhe S., Bedbrook A., Fonseca J., Morais Almeida M., Todo Bom A., Annesi-Maesano I., Caimmi D., Demoly P., Devillier P., Siroux V., Menditto E., Passalacqua G., Stellato C., Ventura M.T., Cruz A.A., Sarquis Serpa F., da Silva J., Larenas-Linnemann D., Rodriguez Gonzalez M., Burguete Cabanas M.T., Bergmann K.C., Keil T., Klimek L., Mosges R., Shamai S., Zuberbier T., Bewick M., Price D., Ryan D., Sheikh A., Anto J.M., Mullol J., Valero A., Haahtela T., Valovirta E., Fokkens W.J., Kuna P., Samolinski B., Bindslev-Jensen C., Eller E., Bosnic-Anticevich S., O'Hehir R.E., Tomazic P.V., Yorgancioglu A., Gemiciloglu B., Bachert C., Hellings P.W., Kull I., Melen E., Wickman M., van Eerd M., De Vries G. The Allergic Rhinitis and its Impact on Asthma (ARIA) score of allergic rhinitis using mobile technology correlates with quality of life: the MASK study. *Allergy* 2018; 73(2): 505-510, <https://doi.org/10.1111/all.13307>.
- [110] Krasilnikova S.V., Eliseeva T.I., Popov K.S., Tush E.V., Khaletskaya O.V., Ovsyannikov D.Y., Balabolkin I.I., Shakhov A.V., Prahov A.V. Multimorbidity of upper respiratory tract pathology in children with bronchial asthma. *Pediatrics* 2018; 97(2): 19-26, <https://doi.org/10.24110/0031-403X-2018-97-2-19-26>.
- [111] Krasilnikova S.V., Eliseeva T.I., Shakhov A.V., Geppe N.A. Capabilities of nasal videoendoscopy in diagnostics of pharyngeal tonsil condition in children with bronchial asthma. *Sovremennye tehnologii v medicine* 2016; 8(3): 126-136, <https://doi.org/10.17691/stm2016.8.3.15>.

- [112] Eliseeva T.I., Krasilnikova S.V., Babaev S.Y., Novozhilov A.A., Ovsyannikov D.Y., Ignatov S.K., Kubysheva N.I., Shakhov A.V. Dependence of anterior active rhinomanometry indices on nasal obstructive disorders in children with atopic bronchial asthma complicated by nasal symptoms. *BioMed Research International* 2018; 2018: 1–10, <https://doi.org/10.1155/2018/1869613>.
- [113] Eliseeva T.I., Krasilnikova S.V., Geppe N.A., Babaev S.Y., Tush E.V., Khaletskaya O.V., Ovsyannikov D.Y., Balabolkin I.I., Ignatov S.K., Kubysheva N.I. Effect of nasal obstructive disorders on sinonasal symptoms in children with different levels of bronchial asthma control. *Canadian Respiratory Journal* 2018; 2018, <https://doi.org/https://doi.org/10.1155/2018/4835823>.
- [114] Krasilnikova S.V., Tush E.V., Babaev S.Y., Khaletskaya A.I., Popov K.S., Novozhilov A.A., Abubakirov T.E., Eliseeva T.I., Ignatov S.K., Shakhov A.V., Kubysheva N.I., Solovyev V.D. Endonasal infrared thermometry for the diagnosis of allergic inflammation of the nasal mucosa in patients with bronchial asthma. *Sovremennye tehnologii v medicine* 2017; 9(4): 201, <https://doi.org/10.17691/stm2017.9.4.25>.
- [115] Bhimrao S.K., Wilson S.J., Howarth P.H. Airway inflammation in atopic patients: a comparison of the upper and lower airways. *Otolaryngol Head Neck Surg* 2011; 145(3): 396–400, <https://doi.org/10.1177/0194599811410531>.
- [116] Lim M.C., Taylor R.M., Naclerio R.M. The histology of allergic rhinitis and its comparison to cellular changes in nasal lavage. *Am J Respir Crit Care Med* 1995; 151(1): 136–144, <https://doi.org/10.1164/ajrccm.151.1.7812543>.
- [117] Eifan A.O., Orban N.T., Jacobson M.R., Durham S.R. Severe persistent allergic rhinitis. inflammation but no histologic features of structural upper airway remodeling. *Am J Respir Crit Care Med* 2015; 192(12): 1431–1439, <https://doi.org/10.1164/rccm.201502-0339oc>.
- [118] Krasilnikova S.V., Eliseeva T.I., Shakhov A.V., Prakhov A.V., Balabolkin I.I. Video endoscopic method of estimation state of nasal and pharyngeal cavity in children with bronchial asthma. *Sovremennye tehnologii v medicine* 2012; 3: 41–45.
- [119] Licari A., Caimmi S., Bosa L., Marseglia A., Marseglia G.L., Caimmi D. Rhinosinusitis and asthma: a very long engagement. *Int J Immunopathol Pharmacol* 2014; 27(4): 499–508, <https://doi.org/10.1177/039463201402700405>.
- [120] Licari A., Brambilla I., De Filippo M., Poddighe D., Castagnoli R., Marseglia G.L. The role of upper airway pathology as a co-morbidity in severe asthma. *Expert Rev Respir Med* 2017; 11(11): 855–865, <https://doi.org/10.1080/17476348.2017.1381564>.
- [121] Fokkens W.J., Lund V.J., Mullol J., Bachert C., Alobid I., Baroody F., Cohen N., Cervin A., Douglas R., Gevaert P., Georgalas C., Goossens H., Harvey R., Hellings P., Hopkins C., Jones N., Joos G., Kalogjera L., Kern B., Kowalski M., Price D., Riechelmann H., Schlosser R., Senior B., Thomas M., Toskala E., Voegels R., Wang de Y., Wormald P.J. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012; 50(1): 1–12, <https://doi.org/10.4193/rhino50e2>.
- [122] Rajan J.P., Wineinger N.E., Stevenson D.D., White A.A. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. *J Allergy Clin Immunol* 2015; 135(3): 676–681.e1, <https://doi.org/10.1016/j.jaci.2014.08.020>.
- [123] Meng J., Zhou P., Liu Y., Liu F., Yi X., Liu S., Holtappels G., Bachert C., Zhang N. The development of nasal polyp disease involves early nasal mucosal inflammation and remodelling. *PLoS One* 2013; 8(12): e82373, <https://doi.org/10.1371/journal.pone.0082373>.
- [124] Martinez-Anton A., Debolos C., Garrido M., Roca-Ferrer J., Barranco C., Alobid I., Xaubet A., Picado C., Mullol J. Mucin genes have different expression patterns in healthy and diseased upper airway mucosa. *Clin Exp Allergy* 2006; 36(4): 448–457, <https://doi.org/10.1111/j.1365-2222.2006.02451.x>.
- [125] Rehl R.M., Balla A.A., Cabay R.J., Hearp M.L., Pytynia K.B., Joe S.A. Mucosal remodeling in chronic rhinosinusitis. *Am J Rhinol* 2007; 21(6): 651–657, <https://doi.org/10.2500/ajr.2007.21.3096>.
- [126] Barham H.P., Osborn J.L., Snidvongs K., Mrad N., Sacks R., Harvey R.J. Remodeling changes of the upper airway with chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2015; 5(7): 565–572, <https://doi.org/10.1002/alr.21546>.